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Efficacy and Safety Assessment of Topical Omega Fatty Acid Product in Experimental Model of Irritant Contact Dermatitis: Randomized Controlled Trial

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Abstract: Contact dermatitis is a common inflammatory skin disease that often requires prescription therapy and is associated with adverse reactions. Omega fatty acids have been recognized for their anti-inflammatory effect and could serve as a safer option in contact dermatitis treatment. Therefore, the aim of this randomized controlled study, conducted at the University of Split School of Medicine, was to evaluate the efficacy and safety of omega fatty acids containing topical products in an experimental model of irritant contact dermatitis. This study was registered with ClinicalTrials (NCT06189144) and is closed. The primary outcomes were levels of transepidermal water loss, skin hydration, and skin erythema, all measured using an MPA6 device in 25 healthy participants. A significant difference was observed between the hydration values of the intervention (45.7 ± 12.4) and control groups (31.6 ± 12.3) ($p < 0.05$) on final measurements (day 10). Moreover, higher erythema levels were observed in participants who were smokers, compared to non-smokers. No adverse drug reactions were observed during the study period. In conclusion, omega fatty acids topical product use shows promise in the treatment of irritant contact dermatitis, and further studies are needed to evaluate efficacy in a larger sample of patients.

Keywords: contact dermatitis; eczema; skin barrier; omega acids; Rilastil; irritant contact dermatitis; randomized controlled trial; transepidermal water loss; erythema; skin hydration

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1. Introduction

Contact dermatitis, an inflammatory skin disease, is characterized by red lesions of the skin which are itchy. These lesions are caused by contact with some external substance. Contact dermatitis, and inflammatory skin diseases in general, significantly impact the affected individuals' quality of life [1,2]. Moreover, these diseases could cause work-related disabilities, financial costs, and social embarrassment. One of the inflammatory skin diseases commonly seen in clinical practice is irritant contact dermatitis. The prevalence of this disease is highly variable worldwide, and this type of dermatitis is mainly caused by the exposure of the skin to an irritant substance, after which damage to the epidermis function occurs. The outer epidermis of the skin serves multiple protective functions, as it controls the permeability of the skin, secretes antimicrobial peptides, includes antioxidants in its extracellular matrix, and secures the physiological hydration levels of the skin [3,4].

In the past, it was believed that irritant contact dermatitis was triggered by direct toxicity of the irritant substance without activation of the immune system. However, later studies have shown that immune-system response is associated with irritant contact dermatitis, and penetration of irritants leads to inflammatory cytokine production by keratinocytes.

This production is followed by the recruitment of immune cells (mast cells, macrophages, etc.) [5]. Therefore, the pharmacotherapy of contact dermatitis includes medicines that target lymphocytes, interleukins, and cytokines. Examples of these medicines are delgocitinib, ruxolitinib, dupilumab, tralokinumab, and small molecule AFX5931. However, all of these drugs are registered for systemic use, which is accompanied by the risk of adverse drug reactions and drug interactions. Some of the reported adverse drug reactions include hypersensitivity reactions, respiratory reactions, and ocular adverse reactions. However, as the majority of these medicines have been marketed in the past few years, the safety profiles will be evaluated in the future, according to adverse drug reaction reports from patients and health care professionals [2].

Even though many therapeutic agents have been evaluated for the treatment of inflammatory skin diseases and their exacerbation, glucocorticoids remain a gold standard in their therapy, and immunomodulatory medications are another option; however, their adverse reactions prevent their wide utilization, and it is necessary to find an effective replacement in clinical practice, e.g., therapies for inflammatory skin disease with a better safety profile [6]. Moisturizing agents have been recognized as an adjuvant therapy in patients with not only contact dermatitis, but also psoriasis and atopic dermatitis. Conversely, not all of the available moisturizers have a role in the improvement of skin barrier function or the effect on the skin's susceptibility to various irritant stimuli [7,8].

Omega polyunsaturated fatty acids have been widely used for their antioxidant and anti-inflammatory effects, mainly as an oral supplement recommended for individuals with chronic non-communicable diseases, such as cardiovascular diseases [9]. However, recent studies shed light on omega use in skin diseases, especially in inflammatory skin diseases such as acne [10], atopic dermatitis [11], and psoriasis [12]. The majority of these studies examined the efficacy of oral use of omega fatty acids, and research on the topical use of products containing omega acids is sparse. Current results suggest that omega-3 fatty acids decrease the production of cytokines involved in inflammation (e.g., interleukin 6) and stimulate Treg cells, which produce anti-inflammatory factors. The stimulation of anti-inflammatory factors in the skin is a proposed mechanism of action for omega-6 fatty acids as well [13].

Therefore, the aim of our study was to evaluate the efficacy and safety of an omega-containing topical formulation in the model of irritant contact dermatitis.

2. Materials and Methods

Our study was designed as a randomized controlled clinical trial. The study setting was the University of Split, School of Medicine, Department of Pharmacy, and it was conducted in June 2023. The Ethics Committee of the University of Split School of Medicine approved the research, and the study was conducted in accordance with ethical principles.

In total, 25 healthy male and female volunteers aged 21 to 29 participated in the research. The subjects had no previously recorded skin diseases. Every participant signed an informed consent before the start of the study. The informed consent form contained information about the aim of the research, the method, and all procedures of its implementation. The exclusion criteria were the following: skin diseases, skin cancers, sun damage in the place intended for examination, use of immunomodulatory medicine, corticosteroids, or antihistamines 30 days before the start of the study, application of emollient cream 3 days before the start of the study, non-compliance with the protocol, excessive exposure to natural or artificial ultraviolet radiation, pregnancy and lactation, history of vitiligo, melasma and other hyperpigmentation or photosensitivity disorders, immunosuppression, and allergy to some of the ingredients of the cream used for the intervention. Before inclusion in the study, participants were also asked if they had ever experienced a side effect from any of the ingredients of the researched cream.

The subjects' forearms were chosen as the test site. On each of the forearms, the place was selected where the irritant dermatitis model would be utilized using a 1% (m/m) sodium lauryl sulfate (SLS) solution. After the baseline skin parameters were measured,

a volume of 60 µL of the solution of SLS was applied to a piece of paper and kept under occlusion for twenty-four hours under twelve-millimeter Finn chambers [14]. Participants were reminded that they should avoid contact with moisture within the above-mentioned period. After removing the Finn's chamber, the test site was washed with water, and the skin parameters were measured again.

After skin damage was inflicted, a computer program in Excel was used to randomly select which forearm would receive the treatment and which would remain untreated. The treatment used was Rilastil Difesa Crema Sterile (Istituto Ganassini, Milan, Italy), which contains omega-3, omega-6, and omega-9 fatty acids. Additionally, 5 mg/cm^2 of the cream was applied twice daily to the selected forearm with at least an eight-hour interval between applications. On measurement days, the first application of the cream was performed by the examiners immediately after measuring skin parameters. The second application, as well as all applications on non-measurement days, was performed by the subjects themselves according to the given instructions. The last application of the cream before measurement had to be at least twelve hours prior to measurement to ensure the accuracy of the Transepidermal Water Loss (TEWL) measurement. All subjects received one tube of the cream. The cream was weighed before the start and after the completion of the study to confirm adherence to the protocol.

Three skin parameters were measured using a non-invasive bioengineering method with the MPA6 device (Courage + Khazaka GmBH, Cologne, Germany), as these parameters were recognized as fundamental for skin barrier assessment. TEWL is an objective measure of the skin barrier, quantified by the amount of water that evaporates through the skin to the external environment [15]. In our study, skin barrier function was determined by measuring TEWL with the Tewameter TM 300 probe (Courage + Khazaka GmBH, Cologne, Germany). The Tewameter® TM 300 probe indirectly measures the water diffusion from the stratum corneum by using two pairs of spatially separated sensors (a relative humidity sensor and a thermometer) that are located inside the hollow cylinder. This open-chamber method measures the evaporation rate and expresses the values in g/m^2 h [16].

The Corneometer CM 825 (Courage + Khazaka GmBH, Cologne, Germany) was used to measure skin hydration. Corneometer® is based on capacitance measurements and is well known for its precision and sensitivity in skin hydration measurements [17,18]. The instrument converts the skin's capacitance values into arbitrary units of skin hydration, which range from 0 to 120 [19]. Skin erythema was measured using the Mexameter MX 18 probe (Courage + Khazaka GmBH, Cologne, Germany). The base of this measurement is the absorption and reflection of light from the skin. A total of 16 light-emitting diodes (LEDs), which are circularly placed on the top of the instrument, emit light at three wavelengths: 568, 660, and 870 nm, which correspond to green, red, and infrared light, respectively. Light that is reflected by the skin is measured by a photo-detector, and the amount of light absorbed by the skin can be calculated. Green and red light are used in erythema measurements to match the hemoglobin's spectral absorption peak [20]. All measurements were conducted in accordance with the guidelines of the Standardization Group of the European Society of Contact Dermatitis [21].

After the objective measurement of skin parameters with the probes, participants were asked about their subjective impressions of using the cream and any potential side effects such as itching, irritation, and similar symptoms. The sites were also examined by a board-certified dermatologist during the study period.

The total duration of the study was eleven days, during which seven measurements were taken. On the first day, the baseline values of the skin parameters were measured, after which a Finn chamber with SLS was applied to the skin. On the second day, after removing the chamber, the values of skin damage were measured, and the intervention was introduced. On the third, fourth, fifth, eighth, and eleventh days, the recovery values of the skin on both arms were measured. On other days of the study, therapy was applied without additional measurements.

Statistical analysis was conducted using IBM SPSS Statistics software (version 25). Two-way ANOVA with repeated measures was used to compare changes over time between the two groups. An Independent Samples t-Test was utilized to compare the means of the two groups at each specific time point. A Paired Samples t-Test was used to compare values within the same group at the beginning and the end of the study. Statistical significance was set at $p < 0.05$. Data are presented as mean ± standard deviation unless stated otherwise.

3. Results

3.1. Demographic Characteristics

In the study, all twenty-five participants were fully measured through all measurement points or days of the study. A greater proportion of the participants in this study were female (80% of all participants). The largest proportion of participants were 24 years old, and all included participants were between 22 and 28 years old (the median age was 24). A greater proportion of participants reported being non-smokers compared to those who used various tobacco products (60% vs. 40%).

3.2. TEWL

The baseline TEWL values were compared between the intervention group and the control group. There was no difference between the baseline values in the control and intervention groups. As shown in Figure 1, TEWL peaked after irritation of the skin with SLS in both the control and intervention groups (41.7 ± 17.1 vs. 42.2 ± 14.6 g m^{-2} h^{-1}, control and intervention). In subsequent measurements, TEWL values decreased until day 7 when they were approximated to the baseline values (19.4 ± 3.7 vs. 18.4 ± 4.83 g m^{-2} h^{-1}, control and intervention). There was no significant difference in magnitude and speed of normalizing TEWL between the groups even with the use of the cream.

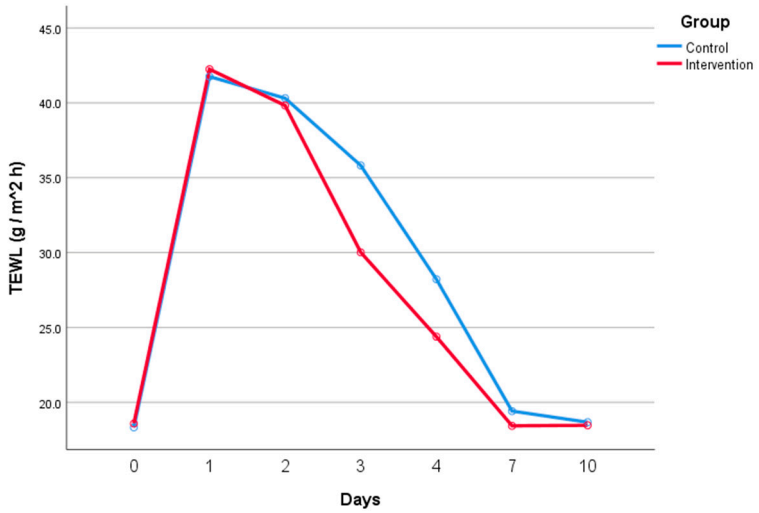

Figure 1. TEWL over the study period represented as two separate curves. One for the control group and a second for the intervention group.

Changes in TEWL over time were also compared between smokers and non-smokers for both the intervention and control groups. Baseline values for smokers and non-smokers were similar for both the control (18.0 ± 6.8 vs. 19.0 ± 5.8 g m^{-2} h^{-1}, non-smokers and smokers) and intervention groups (18.6 ± 4.9 vs. 18.5 ± 4.3 g m^{-2} h^{-1}, non-smokers and smokers). There was no significant difference in TEWL between smokers and non-smokers, neither in the control nor in the intervention group. TEWL values were comparable for both groups for all measurements made. In this study, smoking did not interfere with TEWL recovery after SLS irritation.

3.3. Hydration

Hydration was also compared between the control and intervention groups, and also over time. As seen in Figure 2, both groups had similar baseline values (42.9 ± 8.7 vs. 42.0 ± 6.6 arbitrary units, control and intervention), and both groups experienced a sharp hydration-value decrease after SLS irritation (36.4 ± 11.1 vs. 35.6 ± 11.6 arbitrary units, control and intervention). While the control group's hydration values recovered to the baseline values, the group that used the cream had its hydration values increase over baseline values. Moreover, the use of the cream was shown to keep skin hydrated for a longer period, while the control group had its hydration values decrease again after some time. On day 10, there was a significant difference between the hydration values of the intervention (45.7 ± 12.4 arbitrary units) and control groups (31.6 ± 12.3 arbitrary units) ($p < 0.05$). Respondents' skin was more hydrated when using the cream, compared to not using it.

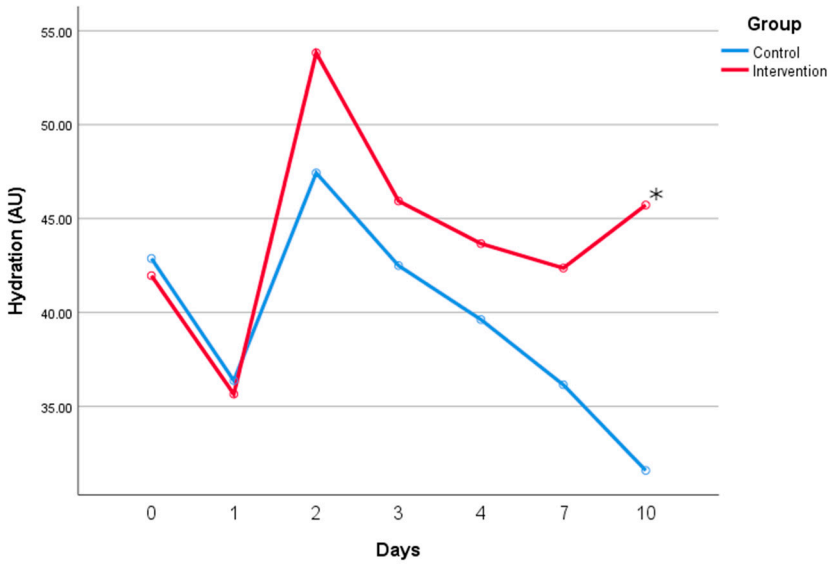

Figure 2. Hydration values over the study period. Comparing control and intervention groups. * Paired Samples *t*-Test.

Hydration values between smokers and non-smokers were also compared for both groups. Figure 3 shows that baseline values for smokers were slightly higher than those values for non-smokers in the control group, but values changed with the same dynamic with no differences based on using tobacco products.

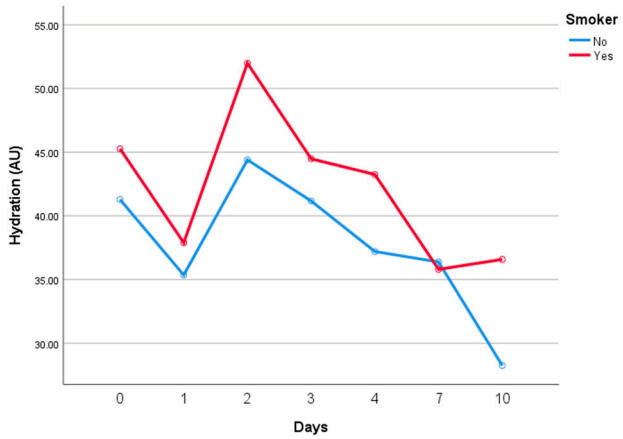

Figure 3. Hydration values over the study period. Comparison between smokers and non-smokers in the control group.

The same comparison was conducted in the intervention group and the result was similar, as seen in Figure 4. There was no significant difference between the hydration values of smokers and non-smokers for the period of the study. Surprisingly, smokers had higher hydration values at day 10, but the difference was not significant (43.8 ± 10.9 vs. 48.6 ± 14.5 arbitrary units, control and intervention). In this study, smoking did not interfere with the hydration values of either group.

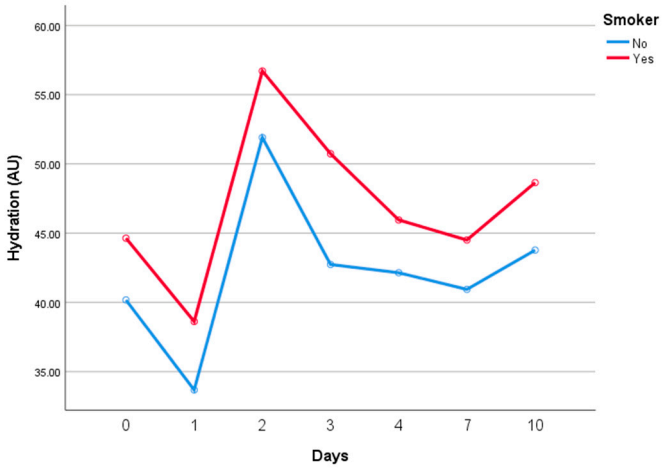

Figure 4. Hydration values over the study period. Comparison between smokers and non-smokers in the intervention group.

3.4. Erythema

Erythema values were measured for 10 days for both the control and intervention groups. There was no significant difference in baseline values between the groups. Values in both groups increased after irritation with SLS, but erythema was more present in the intervention group, compared to the control group, on day 3, as we see in Figure 5 (236.9 ± 58.1 vs. 268.3 ± 51.4 arbitrary units, control and intervention). It took more time for the intervention group to return to baseline erythema values, although there was no significant difference between the groups in any measurement.

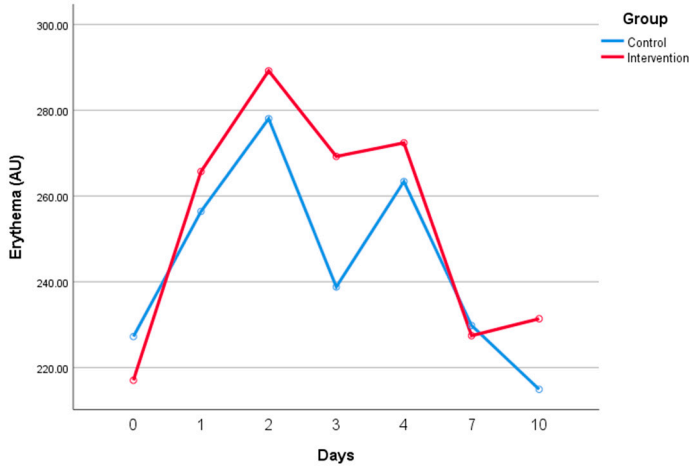

Figure 5. Erythema values over the study period. Comparison between control and intervention groups.

As with previous parameters, erythema values were compared based on the tobacco-using habits of the respondents. Figure 6 illustrates a similar pattern of erythema value changes in both smokers and non-smokers in the control group. There is no significant difference between the groups. However, there was a clear difference between smokers' and non-smokers' erythema presence in the intervention group on day 7 of the

study (207.2 ± 47.5 vs. 251.6 ± 50.5 arbitrary units, control and intervention). Smokers had higher erythema values while using the cream than non-smokers using the cream, as seen in Figure 7 ($p < 0.05$).

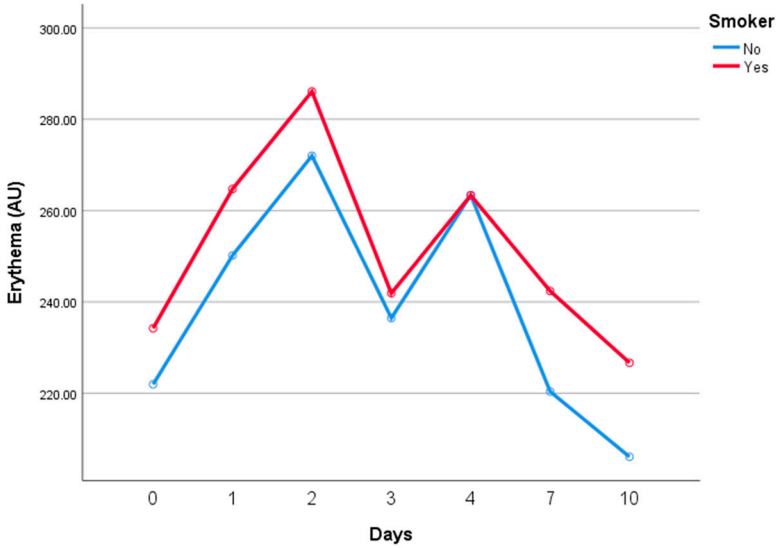

Figure 6. Erythema values over the study period. Comparison between smokers and non-smokers in the control group.

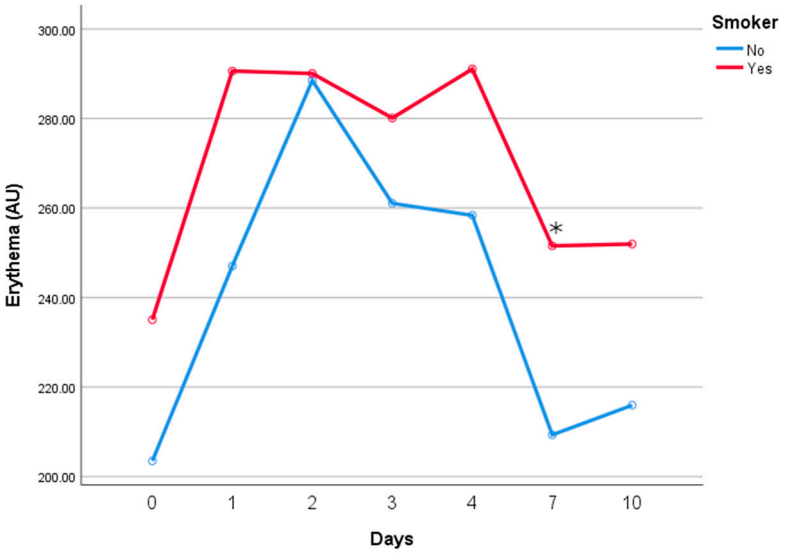

Figure 7. Erythema values over the study period. Comparison between smokers and non-smokers in the intervention group. * Paired Samples *t*-Test.

4. Discussion

To our knowledge, this is one of the first studies examining the efficacy and safety of omega fatty acid topical products in irritant contact dermatitis. After SLS exposure, both the intervention and control groups showed increased TEWL values, decreased hydration levels, and increased erythema values, all of which suggest that the skin barrier function has been impaired. During the study period, TEWL and erythema measurements returned to their baseline values in both groups. However, hydration levels were significantly higher in the group where the Rilastil cream was applied, compared to the control group. Moreover, during the study period, an increase in hydration levels was observed in the intervention group, compared to baseline values. Proper hydration levels of the skin could help maintain skin homeostasis, which is important in individuals affected with

inflammatory skin diseases, but also for the general population [22]. Decreased levels of hydration could affect the ability of the skin to combat free radical-induced oxidative stress and inflammation, all of which could lead to inflammation of the skin, accompanied by the risk of infections and other skin complications. However, additional research is needed to better understand the risk factors that affect inflammation [23–27].

Previous studies on patients with inflammatory skin diseases also reported the positive effect of omega fatty acids on skin hydration levels [13]. For instance, a study by Young Park et al. examined the effect of oral use of primrose oil, which contains omega acid, in acne patients treated with isotretinoin [28]. Isotretinoin is a prescription-only medication used in acne therapy, and it is associated with skin dryness as a common adverse reaction. The results of this study showed an increase in hydration levels in the group of patients who used the oil, compared to the control group. Similar results were found in a study by Brosche et al. on patients with atopic dermatitis [29]. During the study period, participants did not report any adverse reaction to the product, which suggests its acceptable safety profile in the treatment of contact dermatitis. Furthermore, another advantage of this product is its route of application, since its topical therapy is the first-line treatment compared to systemic medications, especially in pediatric patients [30].

Bioactive products such as omega fatty acids, polyphenols, carotenoids, etc., gained popularity in the maintenance of healthy skin [31]. Previous studies have shown that a deficiency of fatty acids results in skin dryness, inflammation, and an increased susceptibility to environmental irritants [32]. One of the most promising omega fatty acids, gamma-linolenic acid, when topically applied, seems to penetrate the skin and maintain the health of the stratum corneum; when taken orally, it enhances the cohesiveness of the dermis and prevents excessive TEWL [33]. Since the results of our study did not show a significant difference between the TEWL values of the intervention and control groups, future studies should include data on circulating omega fatty acid levels in individuals. The hypothesis is that topical treatment would show greater improvement in TEWL measurements in individuals with lower levels of circulating omega fatty acids, and this hypothesis should be further evaluated in future randomized controlled clinical trials. Indeed, a similar observation was found in a study by Marchlewicz et al. where patients with severe psoriasis had a significantly lower concentration of omega-3 and omega-9 compared to patients with less severe psoriasis [34].

The results of our study also showed higher values of erythema in participants who were smokers, both in the intervention and control groups. Smoking is well recognized as a risk factor for skin aging, but the consensus on the effect of smoking on skin barriers has not been reached [35,36]. The results of a cross-sectional study by Alotaibi et al. showed a strong association between smoking and irritant contact dermatitis [37]. Recently, Hergesell et al. examined changes in skin barrier proteins and lipids, and their results showed perturbation of the barrier proteins and lipids, even in the skin areas that were not directly exposed to cigarette smoking [38]. It should be noted that no differences in baseline measurements between smokers and non-smokers were observed in our study. Therefore, future studies should involve a larger sample size of both smokers and non-smokers in order to further evaluate the impact of smoking on skin parameters such as TEWL, hydration levels, and erythema.

This study has some limitations. First of all, it included a small sample size. Nevertheless, since the cream containing omega showed promising results, it seems reasonable to examine it in a larger sample size in the future. Secondly, the intervention cream was applied twice a day, and participants applied the cream on their own; however, to neutralize this possible bias, one application per measurement day was performed under our supervision. Additionally, our study was conducted at one geographic location, with no direct comparison with different population samples. Furthermore, ethnicity could also be a potential variability factor, as it has long been proven that the skin of different ethnic populations can have different compositions and characteristics.

5. Conclusions

The use of omega fatty acid cream in irritant contact dermatitis participants significantly increases the hydration values of the skin, but these results should be confirmed in a larger sample size. Moreover, as skin hydration is essential in all inflammatory skin diseases, further studies could include patients with atopic dermatitis and psoriasis.

Author Contributions: Conceptualization, D.R.; Data Curation, A.S., T.D. and D.V.; Formal Analysis, T.D.; Investigation, M.I. and A.S.; Methodology, D.L., D.V. and J.B. (Josipa Bukic); Software, A.S.P.; Supervision, D.M.; Validation, J.B. (Josko Bozic); Visualization, A.S.P.; Writing—Original Draft, M.I. and J.B. (Josipa Bukic); Writing—Review and Editing, D.L., D.R., D.M. and J.B. (Josko Bozic). All authors have read and agreed to the published version of the manuscript.

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Institutional Review Board Statement: This study was conducted in accordance with the Declaration of Helsinki, and approved by the Ethics Committee of the University of Split School of Medicine (protocol code 2181-98-03-04-23-0030, 23 April 2023).

Informed Consent Statement: Informed consent was obtained from all subjects involved in the study.

Data Availability Statement: Data is available from the corresponding author upon a reasonable request.

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Conflicts of Interest: The authors declare no conflicts of interest.

Abbreviations

The following abbreviations are used in this manuscript:

SLS	Sodium lauryl sulfate
TEWL	Transepidermal water loss

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